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NEWS 1 Web Page URLs for STN Seminar Schedule - N. America
NEWS 2 "Ask CAS" for self-help around the clock
NEWS 3 OCT 23 The Derwent World Patents Index suite of databases on STN has been enhanced and reloaded
NEWS 4 OCT 30 CHEMLIST enhanced with new search and display field
NEWS 5 NOV 03 JAPIO enhanced with IPC 8 features and functionality
NEWS 6 NOV 10 CA/CAplus F-Term thesaurus enhanced
NEWS 7 NOV 10 STN Express with Discover! free maintenance release Version 8.01c now available
NEWS 8 NOV 20 CA/CAplus to MARPAT accession number crossover limit increased to 50,000
NEWS 9 DEC 01 CAS REGISTRY updated with new ambiguity codes
NEWS 10 DEC 11 CAS REGISTRY chemical nomenclature enhanced
NEWS 11 DEC 14 WPIDS/WPINDEX/WPIX manual codes updated
NEWS 12 DEC 14 GBFULL and FRFULL enhanced with IPC 8 features and functionality
NEWS 13 DEC 18 CA/CAplus pre-1967 chemical substance index entries enhanced with preparation role
NEWS 14 DEC 18 CA/CAplus patent kind codes updated
NEWS 15 DEC 18 MARPAT to CA/CAplus accession number crossover limit increased to 50,000
NEWS 16 DEC 18 MEDLINE updated in preparation for 2007 reload
NEWS 17 DEC 27 CA/CAplus enhanced with more pre-1907 records
NEWS 18 JAN 08 CHEMLIST enhanced with New Zealand Inventory of Chemicals
NEWS 19 JAN 16 CA/CAplus Company Name Thesaurus enhanced and reloaded
NEWS 20 JAN 16 IPC version 2007.01 thesaurus available on STN
NEWS 21 JAN 16 WPIDS/WPINDEX/WPIX enhanced with IPC 8 reclassification data
NEWS 22 JAN 22 CA/CAplus updated with revised CAS roles
NEWS 23 JAN 22 CA/CAplus enhanced with patent applications from India
NEWS 24 JAN 29 PHAR reloaded with new search and display fields
NEWS 25 JAN 29 CAS Registry Number crossover limit increased to 300,000 in multiple databases
NEWS 26 FEB 13 CASREACT coverage to be extended
NEWS 27 Feb 15 PATDPASPC enhanced with Drug Approval numbers
NEWS 28 Feb 15 RUSSIAPAT enhanced with pre-1994 records
NEWS 29 Feb 23 KOREAPAT enhanced with IPC 8 features and functionality
NEWS 30 Feb 26 MEDLINE reloaded with enhancements
NEWS 31 Feb 26 EMBASE enhanced with Clinical Trial Number field
NEWS 32 Feb 26 TOXCENTER enhanced with reloaded MEDLINE
NEWS 33 Feb 26 IFICDB/IFIPAT/IFIUDB reloaded with enhancements
NEWS 34 Feb 26 CAS Registry Number crossover limit increased from 10,000 to 300,000 in multiple databases

NEWS EXPRESS NOVEMBER 10 CURRENT WINDOWS VERSION IS V8.01c, CURRENT MACINTOSH VERSION IS V6.0c(ENG) AND V6.0Jc(JP), AND CURRENT DISCOVER FILE IS DATED 25 SEPTEMBER 2006.

NEWS HOURS STN Operating Hours Plus Help Desk Availability
NEWS LOGIN Welcome Banner and News Items

```
 NEWS IPC8      For general information regarding STN implementation of IPC 8
 NEWS X25       X.25 communication option no longer available

Enter NEWS followed by the item number or name to see news on that
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=> file reg
COST IN U.S. DOLLARS                                    SINCE FILE      TOTAL
                                                          ENTRY     SESSION
FULL ESTIMATED COST                                        0.21        0.21

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STRUCTURE FILE UPDATES:     5 MAR 2007  HIGHEST RN 924962-30-1
DICTIONARY FILE UPDATES:    5 MAR 2007  HIGHEST RN 924962-30-1

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REGISTRY includes numerically searchable data for experimental and
predicted properties as well as tags indicating availability of
experimental property data in the original document.  For information
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http://www.cas.org/ONLINE/UG/regprops.html

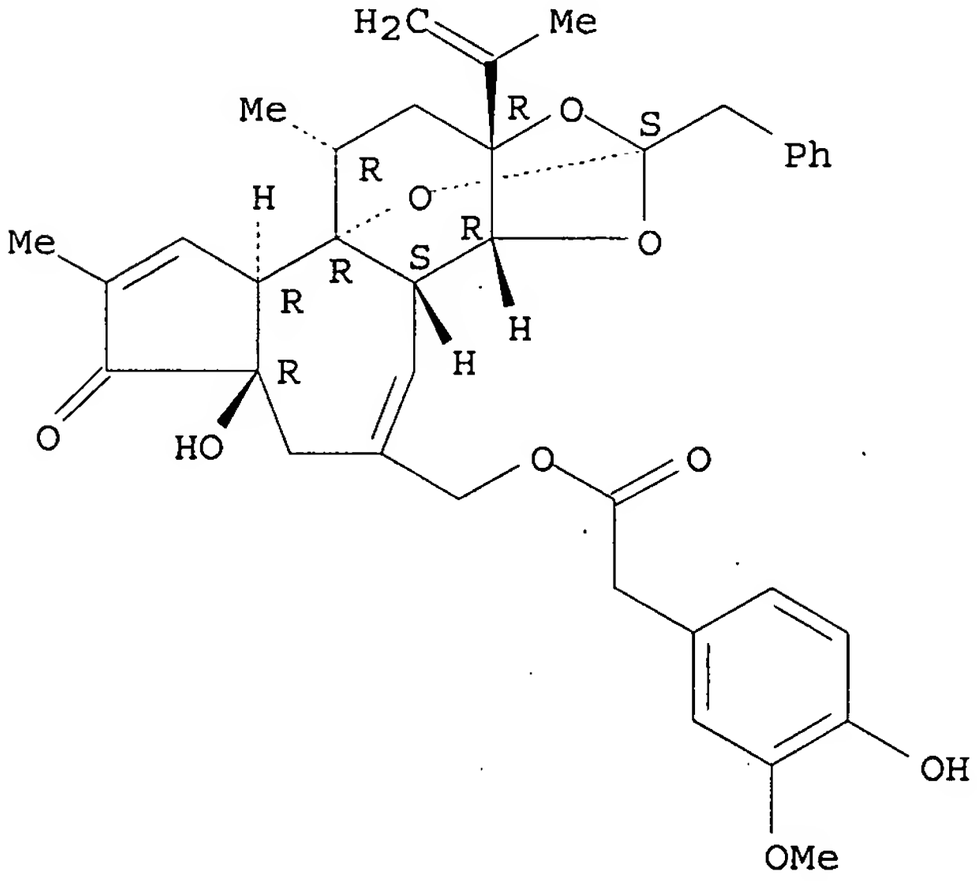
=> s resiniferatoxin/cn
L1             1 RESINIFERATOXIN/CN

=> d l1

L1   ANSWER 1 OF 1  REGISTRY  COPYRIGHT 2007 ACS on STN
RN   57444-62-9  REGISTRY
ED   Entered STN:  16 Nov 1984
CN   Benzeneacetic acid, 4-hydroxy-3-methoxy-, [(2S,3aR,3bS,6aR,9aR,9bR,10R,11a
     R)-3a,3b,6,6a,9a,10,11,11a-octahydro-6a-hydroxy-8,10-dimethyl-11a-(1-
     methylethenyl)-7-oxo-2-(phenylmethyl)-7H-2,9b-epoxyazuleno[5,4-e]-1,3-
     benzodioxol-5-yl]methyl ester (9CI)  (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN   Daphnetoxin, 6,7-deepoxy-6,7-didehydro-5-deoxy-21-dephenyl-21-
     (phenylmethyl)-, 20-(4-hydroxy-3-methoxybenzeneacetate)
OTHER NAMES:
CN   (+)-Resiniferatoxin
CN   Benzeneacetic acid, 4-hydroxy-3-methoxy-, [3a,3b,6,6a,9a,10,11,11a-
     octahydro-6a-hydroxy-8,10-dimethyl-11a-(1-methylethenyl)-7-oxo-2-
```

(phenylmethyl)-7H-2,9b-epoxyazuleno[5,4-e]-1,3-benzodioxol-5-yl]methyl
ester, [2S-(2α,3aβ,3bβ,6aβ,9aα,9bα,10.alp
ha.,11aβ)]-
CN Resiniferatoxin
FS STEREOSEARCH
MF C37 H40 O9
CI COM
LC STN Files: ADISINSIGHT, ADISNEWS, AGRICOLA, ANABSTR, BEILSTEIN*, BIOSIS,
BIOTECHNO, CA, CAPLUS, CASREACT, CHEMCATS, CIN, CSCHEM, EMBASE,
IMSDRUGNEWS, IMSRESEARCH, IPA, MEDLINE, MSDS-OHS, NAPRALERT, PROMT,
RTECS*, SYNTHLINE, TOXCENTER, USPAT2, USPATFULL
(*File contains numerically searchable property data)

Absolute stereochemistry.



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

350 REFERENCES IN FILE CA (1907 TO DATE)
17 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
352 REFERENCES IN FILE CAPLUS (1907 TO DATE)

=> s tinyatoxin
L2 1 TINYATOXIN

=> d l2

L2 ANSWER 1 OF 1 REGISTRY COPYRIGHT 2007 ACS on STN
RN 58821-95-7 REGISTRY
ED Entered STN: 16 Nov 1984
CN Benzeneacetic acid, 4-hydroxy-, [(2S,3aR,3bS,6aR,9aS,9bR,10R,11aR)-
3a,3b,6,6a,9a,10,11,11a-octahydro-6a-hydroxy-8,10-dimethyl-11a-(1-
methylethenyl)-7-oxo-2-(phenylmethyl)-7H-2,9b-epoxyazuleno[5,4-e]-1,3-
benzodioxol-5-yl]methyl ester (9CI) (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN 7H-2,9b-Epoxyazuleno[5,4-e]-1,3-benzodioxole, daphnetoxin deriv.
CN Daphnetoxin, 6,7-deepoxy-6,7-didehydro-5-deoxy-21-dephenyl-21-
(phenylmethyl)-, 20-(4-hydroxybenzeneacetate)
OTHER NAMES:
CN Benzeneacetic acid, 4-hydroxy-, [3a,3b,6,6a,9a,10,11,11a-octahydro-6a-

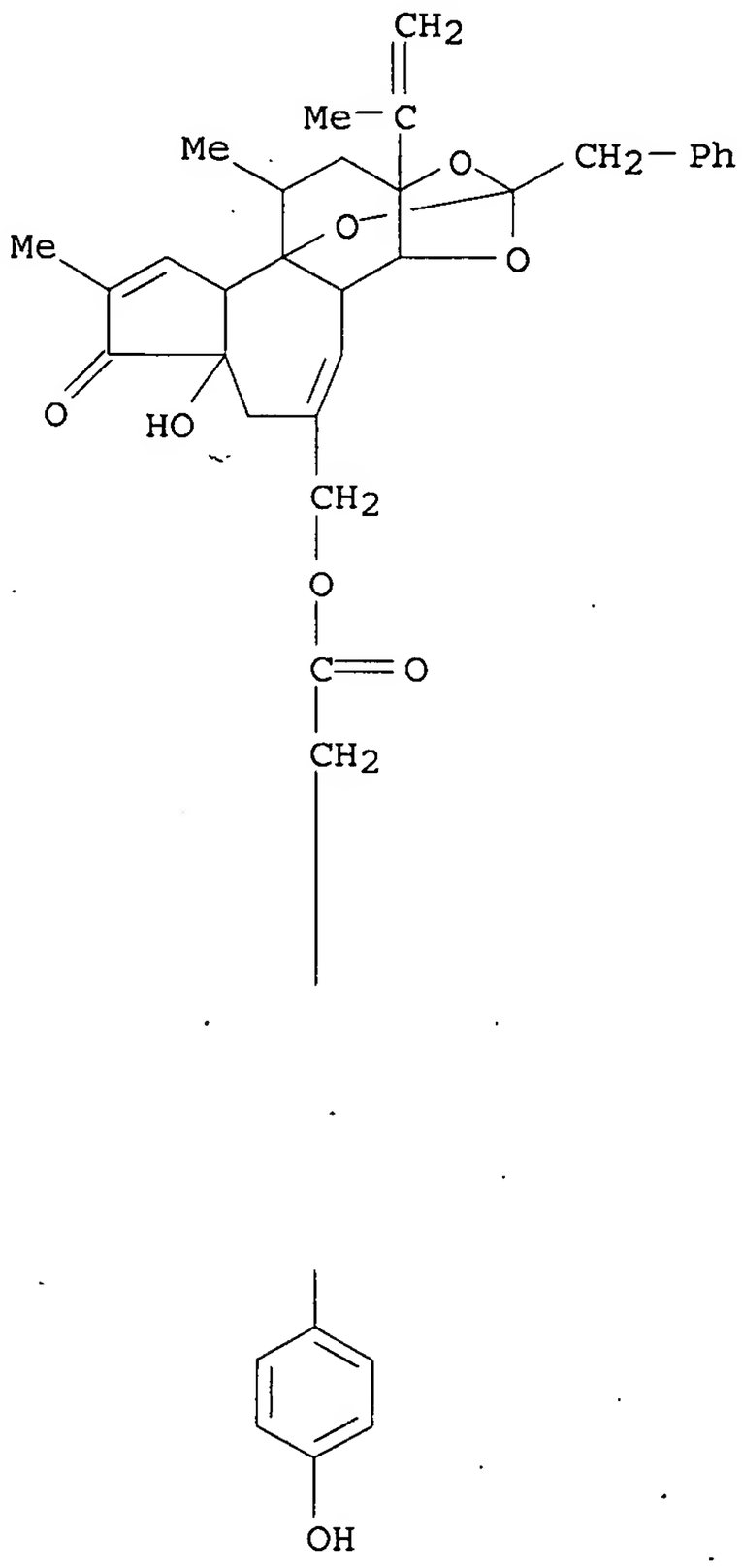
hydroxy-8,10-dimethyl-11a-(1-methylethenyl)-7-oxo-2-(phenylmethyl)-7H-2,9b-epoxyazuleno[5,4-e]-1,3-benzodioxol-5-yl]methyl ester, [2S-(2α,3aβ,3bβ,6aβ,9aα,9bα,10α,11aβ)]-

CN Tinyatoxin

MF C36 H38 O8

LC STN Files: BEILSTEIN*, BIOSIS, BIOTECHNO, CA, CAPLUS, CHEMCATS, CSCHEM, EMBASE, MEDLINE, NAPRALERT, RTECS*, TOXCENTER, USPAT2, USPATFULL
(*File contains numerically searchable property data)

PAGE 1-A



PAGE 2-A

PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

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32 REFERENCES IN FILE CAPLUS (1907 TO DATE)

```
=> s 20-homovanillyl-mezerein
        536628 20
            12 HOMOVANILLYL
             5 MEZEREIN
L3           1 20-HOMOVANILLYL-MEZEREIN
                 (20(W)HOMOVANILLYL(W)MEZEREIN)
```

```
=> s l3
        536628 20
            12 HOMOVANILLYL
             5 MEZEREIN
L4           1 20-HOMOVANILLYL-MEZEREIN
                 (20(W)HOMOVANILLYL(W)MEZEREIN)

=> d l3

L3   ANSWER 1 OF 1  REGISTRY  COPYRIGHT 2007 ACS on STN
RN   126584-64-3  REGISTRY
ED   Entered STN:  20 Apr 1990
CN   Benzeneacetic acid, 4-hydroxy-3-methoxy-, [(2S,3aR,3bS,3cS,4aR,5S,5aS,8aR,
     8bR,9R,10S)-3a,3b,3c,5,5a,6,8a,9,10,10a-decahydro-5,5a-dihydroxy-7,9-
     dimethyl-10a-(1-methylethenyl)-6-oxo-10-[[(2E,4E)-1-oxo-5-phenyl-2,4-
     pentadienyl]oxy]-2-phenyl-4aH-2,8b-epoxyoxireno[6,7]azuleno[5,4-e]-1,3-
     benzodioxol-4a-yl]methyl ester (9CI)  (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN   6H-2,8b-Epoxyoxireno[6,7]azuleno[5,4-e]-1,3-benzodioxole, daphnetoxin
     deriv.
CN   Daphnetoxin, 12-[(1-oxo-5-phenyl-2,4-pentadienyl)oxy]-,
     20-(4-hydroxy-3-methoxybenzeneacetate), [12β(2E,4E)]-
OTHER NAMES:
CN   20-Homovanillylmezerein
DR   126347-68-0
MF   C47 H46 O13
SR   CA
LC   STN Files:   CA, CAPLUS, TOXCENTER, USPAT2, USPATFULL
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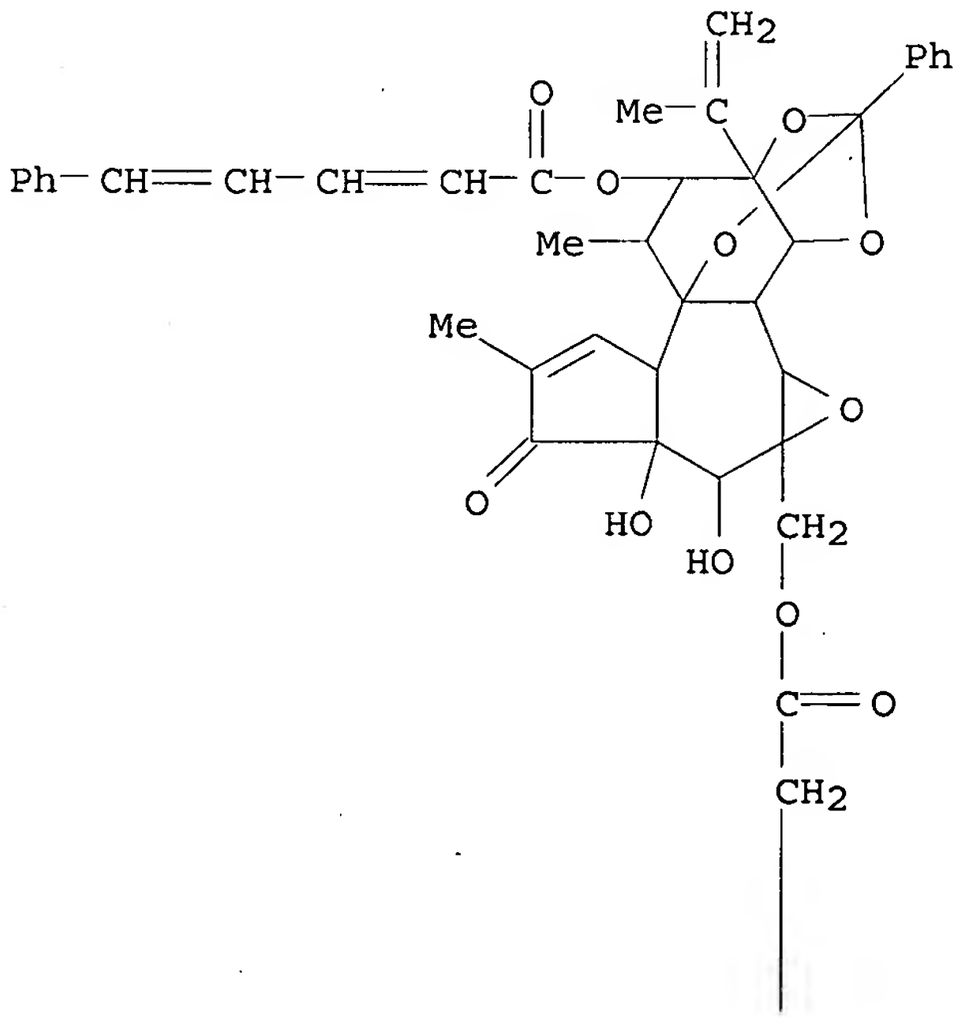

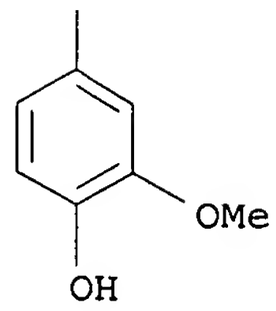

PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

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4 REFERENCES IN FILE CAPLUS (1907 TO DATE)

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=> s 20-homovanillyl-12-deoxyphorbol-13-phenylacetate
        536628 20
            12 HOMOVANILLYL
        862508 12
            28 DEOXYPHORBOL
        686842 13
          2746 PHENYLACETATE
L5           1 20-HOMOVANILLYL-12-DEOXYPHORBOL-13-PHENYLACETATE
               (20(W)HOMOVANILLYL(W)12(W)DEOXYPHORBOL(W)13(W)PHENYLACETATE)

=> d l5

L5   ANSWER 1 OF 1  REGISTRY  COPYRIGHT 2007 ACS on STN
RN   126584-63-2  REGISTRY
ED   Entered STN:  20 Apr 1990
CN   Benzeneacetic acid, 4-hydroxy-3-methoxy-, [(1aR,1bS,4aR,7aS,7bR,8R,9aS)-
     1a,1b,4,4a,5,7a,7b,8,9,9a-decahydro-4a,7b-dihydroxy-1,1,6,8-tetramethyl-5-
     oxo-9a-[(phenylacetyl)oxy]-1H-cyclopropa[3,4]benz[1,2-e]azulen-3-yl]methyl
     ester (9CI)  (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN   1H-Cyclopropa[3,4]benz[1,2-e]azulene, benzeneacetic acid deriv.
CN   Benzeneacetic acid, 4-hydroxy-3-methoxy-, [1a,1b,4,4a,5,7a,7b,8,9,9a-
     decahydro-4a,7b-dihydroxy-1,1,6,8-tetramethyl-5-oxo-9a-[(phenylacetyl)oxy]-
     1H-cyclopropa[3,4]benz[1,2-e]azulen-3-yl]methyl ester,
     [1aR-(1aα,1bβ,4aβ,7aα,7bα,8α,9aα)]-
OTHER NAMES:
CN   20-Homovanillyl-12-deoxyphorbol 13-phenylacetate
FS   STEREOSEARCH
DR   126320-73-8
MF   C37 H42 O9
SR   CA
LC   STN Files:   CA, CAPLUS, TOXCENTER, USPAT2, USPATFULL

Absolute stereochemistry.
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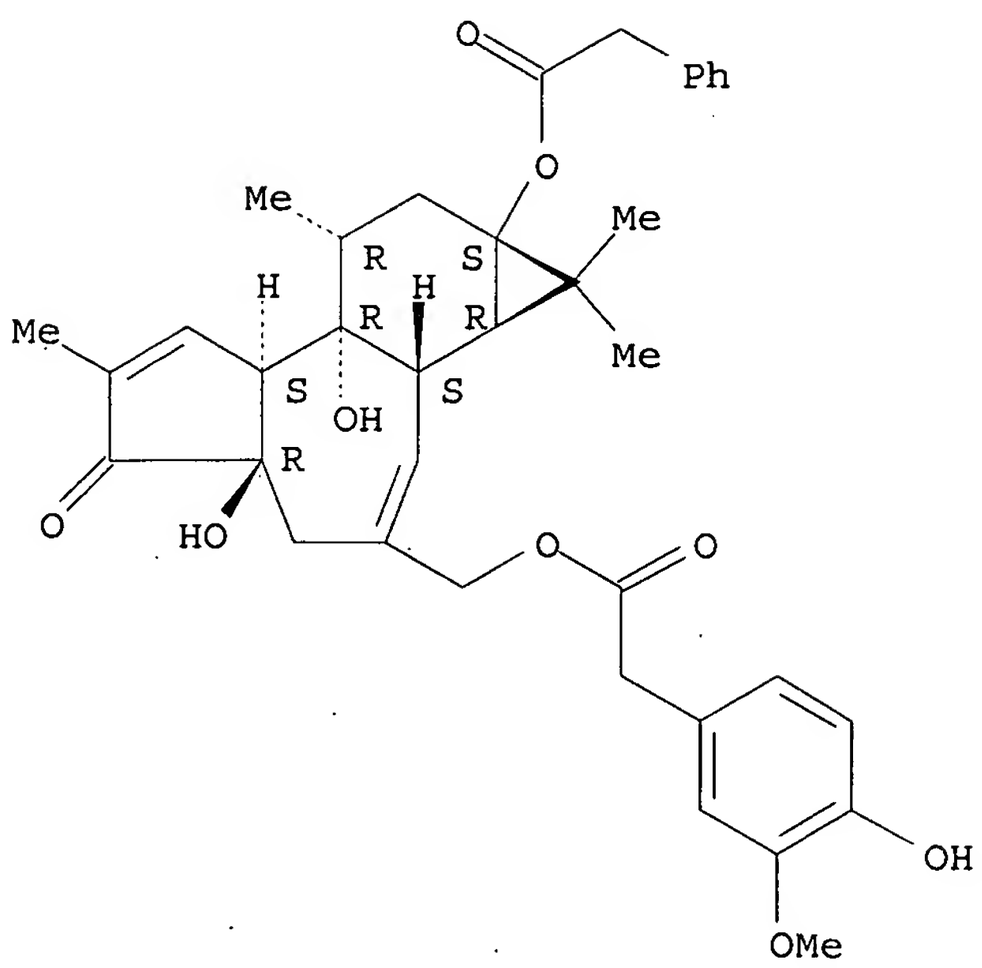

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=> file medicine
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FILE 'USPAT2' ENTERED AT 19:50:26 ON 06 MAR 2007
CA INDEXING COPYRIGHT (C) 2007 AMERICAN CHEMICAL SOCIETY (ACS)

=> s l1 or l2 or l3 or l5
'CN' IS NOT A VALID FIELD CODE
'CN' IS NOT A VALID FIELD CODE
'CN' IS NOT A VALID FIELD CODE
'CN' IS NOT A VALID FIELD CODE
'CN' IS NOT A VALID FIELD CODE
  12 FILES SEARCHED...
'CN' IS NOT A VALID FIELD CODE
'CN' IS NOT A VALID FIELD CODE
'CN' IS NOT A VALID FIELD CODE
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'CN' IS NOT A VALID FIELD CODE
'CN' IS NOT A VALID FIELD CODE
'CN' IS NOT A VALID FIELD CODE
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'CN' IS NOT A VALID FIELD CODE
'CN' IS NOT A VALID FIELD CODE
L6         2615 L1 OR L2 OR L3 OR L5

=> s l6 and urinary incontinence
L7          145 L6 AND URINARY INCONTINENCE

=> s l7 not py>1998
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  15 FILES SEARCHED...
  27 FILES SEARCHED...
  28 FILES SEARCHED...
L8            8 L7 NOT PY>1998

=> d l8 1-8 bib, abs
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In a multifile environment, each file must have at least one valid
format requested.  Refer to file specific help messages or the
STNGUIDE file for information on formats available in individual
files.
REENTER DISPLAY FORMAT FOR ALL FILES (FILEDEFAULT):1-8
'1-8' IS NOT A VALID FORMAT
In a multifile environment, a format can only be used if it is valid
in at least one of the files.  Refer to file specific help messages
or the STNGUIDE file for information on formats available in
individual files.
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'L113' IS NOT A VALID FORMAT
In a multifile environment, a format can only be used if it is valid
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in at least one of the files.  Refer to file specific help messages
or the STNGUIDE file for information on formats available in
individual files.
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In a multifile environment, a format can only be used if it is valid
in at least one of the files.  Refer to file specific help messages
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individual files.
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'1-8' IS NOT A VALID FORMAT
In a multifile environment, a format can only be used if it is valid
in at least one of the files.  Refer to file specific help messages
or the STNGUIDE file for information on formats available in
individual files.
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In a multifile environment, a format can only be used if it is valid
in at least one of the files.  Refer to file specific help messages
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individual files.
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In a multifile environment, each file must have at least one valid
format requested.  Refer to file specific help messages or the
STNGUIDE file for information on formats available in individual
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format requested.  Refer to file specific help messages or the
STNGUIDE file for information on formats available in individual
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NO VALID FORMATS ENTERED FOR FILE 'IMSDRUGNEWS'
In a multifile environment, each file must have at least one valid
format requested.  Refer to file specific help messages or the
STNGUIDE file for information on formats available in individual
files.
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'L113' IS NOT A VALID FORMAT
'1-8' IS NOT A VALID FORMAT
In a multifile environment, a format can only be used if it is valid
in at least one of the files.  Refer to file specific help messages
or the STNGUIDE file for information on formats available in
individual files.
REENTER DISPLAY FORMAT FOR ALL FILES (FILEDEFAULT):all

L8   ANSWER 1 OF 8  ADISINSIGHT COPYRIGHT (C) 2007  Adis Data Information BV on
     STN
AN   1998:8900  ADISINSIGHT
SO   Adis R&D Insight
DN   009782
CDAT Jul 11, 2006
CN   Resiniferatoxin
CN   RTX
CN   Benzeneacetic acid, 4-hydroxy-3-methoxy-, ((2S,3aR,3bS,6aR,9aR,9bR,10R,11a
     R)-3a,3b,6,6a,9a,10,11,11a-octahydro-6a-hydroxy-8,10-dimethyl-11a-(1-
     methylethenyl)-7-oxo-2-(phenylmethyl)-7H-2,9b-epoxyazuleno(5,4-e)-1,3-
     benzodioxol-5-yl)methyl ester
MF   C37 H40 O9
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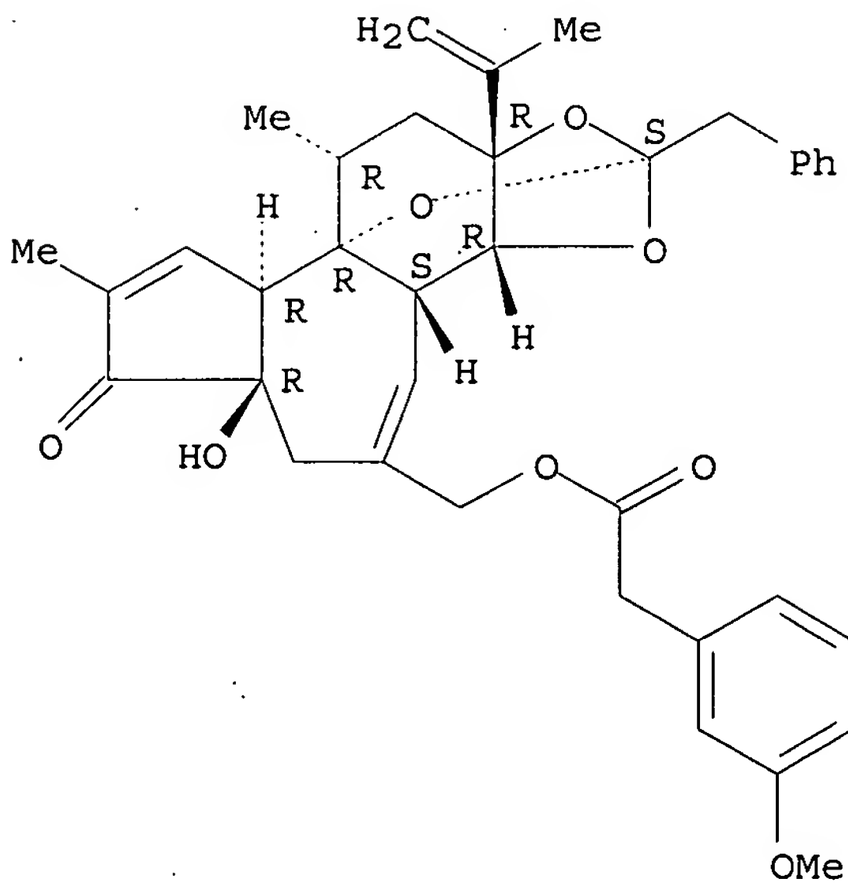
RN 57444-62-9
STR

Absolute stereochemistry.



CC EPHMRA ATC CODE: G4B4 Urinary incontinence products; R3 Anti-Asthma and COPD Products
CC WHO ATC CODE: G04B-D Urinary antispasmodics; R03 Drugs for Obstructive Airway Diseases
HDP Discontinued II
DSTA Discontinued II, Canada, Interstitial cystitis
Discontinued II, Europe, Overactive bladder
Discontinued II, United States, Overactive bladder
Discontinued I, Europe, Rhinitis
Discontinued Clinical, United Kingdom, Overactive bladder
ORIGINATOR: National Institutes of Health (United States)
PARENT: National Institutes of Health (USA)
LICENSEE: Afferon Corporation; ICOS Corporation
OS 800818786; 800818678; 800970648; 800911494
WC 948

TX TEXT
Introduction:
Resiniferatoxin (RTX(TM)), a vanilloid that is chemically related to capsaicin, was synthesised from a raw material derived from the African cactus Euphorbia resinifera. Resiniferatoxin is a small molecule that can be delivered directly into the bladder through a catheter to desensitise afferent nerve fibres (C-fibres).

Company agreements
Licensing agreements: Afferon Corporation originally licensed resiniferatoxin from the US National Institutes of Health. In November 2001, Afferon announced that ICOS Corporation had licensed exclusive worldwide rights to resiniferatoxin for urological indications, previous agreement with MundiPharma was terminated. ICOS was to pay an initial fee, and was also to make milestone and royalty payments to Afferon. ICOS was also to be responsible for development and commercialisation costs for resiniferatoxin and its analogues.
In May 1999, resiniferatoxin was exclusively licensed to Mundipharma International for marketing and clinical development as a treatment for overactive bladder in the Middle East and Europe. However, this agreement

between Afferon and Mundipharma was terminated.

Key development milestones
Overactive bladder: ICOS Corporation was investigating intracavernous resiniferatoxin in phase I/II trials of overactive bladder. However, development of resiniferatoxin has been discontinued.

Positive results of intravesical administration of resiniferatoxin in patients with frequency and urgency due to increased bladder sensation were reported at the 100th Annual Meeting of the American Urological Association (AUA-2005).

Interstitial cystitis: in the fourth quarter of 2003, ICOS completed patient follow-up in a phase II clinical trial for the treatment of interstitial cystitis in Canada. The objective of this trial was to evaluate resiniferatoxin's potential in reducing bladder pain, nocturia and urinary frequency and improve the quality of life in patients with interstitial cystitis. In January 2004, ICOS determined that resiniferatoxin was not effective in relieving patients' symptoms. Due to these results, ICOS discontinued development of resiniferatoxin for the treatment of interstitial cystitis.

Non-allergic rhinitis: a phase I/II trial with resiniferatoxin for the treatment of non-allergic rhinitis was scheduled to commence in Europe in the fourth quarter of 2002.

TX PHARMACOLOGY OVERVIEW:
Pharmacodynamics:
Urinary urge-curbing effects
Mechanism of action:
Vanilloid receptor agonists

TX CLINICAL OVERVIEW:
Route(s) of Administration: Intracavernous, Intravesicular
Administration Freq.(per day):
Adverse events:
occasional: Pain.
rare: Constipation, Cystitis, Diaphoresis, Mucosal disorders.
Drug Interactions:
Unknown.

TX Adverse Events:
In an open-label phase I/II trial in 14 patients, resiniferatoxin administration was not associated with any clinically significant treatment-related adverse effects/1/. The most common adverse effects associated with intravesical instillation of a single dose of resiniferatoxin (0.005-1 micromol/L) were pain during instillation, mucosal erythema, cystitis, diaphoresis, autonomic dysreflexia and constipation. However, the drug was generally well tolerated and no long-term sequelae were reported in this study. Severity of instillation pain did not correlate with dose/2/.
No warmth or burning was reported during intravesicular instillation of resiniferatoxin (3 times 10 sup(-4) mol) in a study in 12 patients with interstitial cystitis. There were no serious adverse events/3/.
In a phase II, randomised, double-blind study, resiniferatoxin appeared to be better tolerated than capsaicin in patients with detrusor hyperreflexia associated with spinal cord disorders. The incidence of adverse events tended to be lower in resiniferatoxin recipients compared with capsaicin recipients (43% vs 72% of patients). The incidence of suprapubic pain was significantly higher in capsaicin recipients (50% vs 19% of resiniferatoxin recipients; $p < 0.05$)/4/.

TX THERAPEUTIC TRIALS:
Genitourinary Disorders:
Detrusor instability: resiniferatoxin (0.5 or 1.0 micromol/L)

significantly reduced incontinence episodes per day and increased cystometric capacity at 1 and 3 weeks, relative to baseline, in a dose-escalation study in 36 patients. Neither placebo nor resiniferatoxin doses of < 0.2 micromol/L had any significant effect. A single dose of either placebo or resiniferatoxin (0.005-1 micromol/ L) was administered by intravesical instillation/2/.

In a phase II, randomised, double-blind study, resiniferatoxin and capsaicin were equally effective in the treatment of urinary incontinence in patients with detrusor hyperreflexia associated with spinal cord disorders. On day 30, clinical response rates were 80% and 78%, respectively, and urodynamic response rates were 60% and 83%, respectively/4/.

Interstitial cystitis: nocturia, urinary frequency and pain were significantly reduced in 12 patients 30 days after intravesicular instillation of resiniferatoxin (3 times 10 sup(-4) mol). However, 90 days after treatment, these parameters had returned to approximately baseline values/3/.

Neurogenic bladder: resiniferatoxin and capsaicin administered intravesically have been shown to improve urinary symptoms and bladder capacity in patients with detrusor instability. Resiniferatoxin differs in its chemical structure to capsaicin and is about 1000-fold more potent. An open-label phase II study investigated the comparative efficacy and tolerability of intravesical single-dose capsaicin 2 mmol/L versus resiniferatoxin 100 nmol/L in 24 chronic spinal cord injury patients with detrusor instability refractory to oral oxybutynin therapy. Resiniferatoxin provided superior clinical and urodynamic benefits compared with baseline, and had fewer side effects than intravesical capsaicin over 90 days of follow-up/5/.

Overactive bladder: intravesical administration of resiniferatoxin induced significant, sustained improvements in lower urinary tract symptoms (LUTS) and urodynamic parameters in patients with urgency and frequency due to increased bladder sensation (formerly known as sensory urgency). A total of 15 such patients were treated. Following pre-treatment analgesia, patients' bladders were emptied and then administered a single intravesical instillation of 100mL of resiniferatoxin 50nM. Patients were assessed at 1, 3 and 6 months. Fourteen patients (93.3%) were considered responders to resiniferatoxin (defined as having a > 50% improvement in at least one urodynamic or LUTS parameter in the first follow-up). Nine patients who completed 6 months' follow-up showed significant improvements from baseline in volume at first desire to void (FD vol), mean micturition volume (MMV), 24-hour frequency and daytime frequency. A significant improvement in the maximum cystometric capacity (MCC) at 3 months' follow-up was also seen. There was no change in the degree of incontinence in the six patients who were incontinent prior to treatment. Of the seven patients with bladder pain, a `very good' response was achieved by five patients at 1 month's follow-up, by three patients at 3 months' follow-up, and by one patient at 6 months' follow-up/6/.

RDAT	RNTE
08 Nov 2001	ICOS Corporation has licensed exclusive worldwide rights to develop resiniferatoxin for urological indications
19 Jul 2000	A study has been added to the adverse events and Genitourinary Disorders therapeutic trials sections (818678)
18 Jul 2000	A study has been added to the adverse events and Genitourinary Disorders therapeutic trials sections (818786)
01 Mar 2000	Afferon and Mundipharma have initiated a phase II trial in patients with overactive bladder in Europe
15 Jul 1999	Afferon has received approval for the initiation of phase II trials in patients with overactive bladder in the UK and France
06 Jul 1999	Profile reviewed by Afferon Corporation

07 May 1999 Resiniferatoxin is licensed to Mundipharma for bladder indications in Europe and the Middle East
17 Mar 1998 Phase-II clinical trials for Diabetic neuropathies in USA (Unknown route)
10 Feb 1998 New profile
10 Feb 1998 Phase-II clinical trials for Overactive bladder in Europe (Intracavernous)
10 Feb 1998 Phase-II clinical trials for Overactive bladder in USA (Intracavernous)

RE 1. Afferon Corporation. Afferon Corporatin announces positive preliminary results of phase I/II European clinical trials of RTX for urge incontinence. Media Release. : (2 pages), 16 Sep 1998. (English).
2. Rivas DA, Shenot PJ, et al. Intravesical resiniferatoxin improves bladder capacity and decreases incontinence in patients with refractory detrusor hyperreflexia: a multicenter, blinded, randomized, placebo-controlled trial. Journal of Urology. 163 (Suppl.): 244 (plus poster and oral presentation), Apr 2000. (English). 800818786
3. Lazzeri M, Beneforti P, et al. Single dose of intravesical resiniferatoxin for the treatment of interstitial cystitis -preliminary results of a randomised controlled study. Journal of Urology. 163 (Suppl.): 60 (plus poster), Apr 2000. (English). 800818678
4. de Seze M, Wiart L, et al. Intravesical capsaicin versus resiniferatoxin for the treatment of detrusor hyperreflexia in spinal cord injured patients: a double-blind, randomized, controlled study. Journal of Urology. 171: 251-255, No. 1, Jan 2004. (English). 800970648
5. Giannantoni A, Di Stasi SM, et al. Intravesical capsaicin versus resiniferatoxin in patients with detrusor hyperreflexia: a prospective randomized study. Journal of Urology. 167: 1710-1714, Apr 2002. (English). 800911494
6. Apostolidis A, Gonzales G, et al. Intravesical resiniferatoxin improves lower urinary tract symptoms and urodynamic parameters in patients with urgency and frequency due to increased bladder sensation. European Urology Supplements. 4: 142, No. 3, Mar 2005. (English).

L8 ANSWER 2 OF 8 BIOTECHNO COPYRIGHT 2007 Elsevier Science B.V. on STN
AN 1998:28369399 BIOTECHNO
TI Use of intravesical capsaicin for urge urinary incontinence and irritative voiding syndromes
AU Hussain I.F.; Fowler C.J.
CS I.F. Hussain, Department of Uro-Neurology, Natl Hospital Neurology Neurosurgery, Queen Square, London WC1N 3BZ, United Kingdom. E-mail: i.hussain@ion.ucl.ac.uk
SO Current Opinion in Urology, (1998), 8/4 (293-296), 23 reference(s) CODEN: CUOUEQ ISSN: 0963-0643
DT Journal; (Short Survey)
CY United Kingdom
LA English
SL English
AB Intravesical capsaicin has been used in the management of selected patients with urge urinary incontinence throughout this decade, but the past 12 months has seen considerable interest in this and related compounds. It is no coincidence that during the same period the capsaicin receptor was cloned and named the vanilloid receptor subtype 1 and the European dual centre study of intravesical capsaicin reported that overall 80% of patients derived some clinical benefit. In spite of this, ultrapotent capsaicin analogues such as resiniferatoxin, which also interact with the vanilloid receptor subtype 1, are being studied. Preliminary reports of the potential advantages of intravesical resiniferatoxin are beginning to emerge, and in the future drugs that manipulate the vanilloid receptor may become universally important in the management of neurogenic overactive bladders.
CT *capsaicin; *urge incontinence; *micturition; vanilloid receptor; resiniferatoxin; lidocaine; alcohol; neurogenic bladder; muscle spindle afferent nerve; desensitization; spinal cord injury; multiple sclerosis;

detrusor dyssynergia; bladder capacity; bladder pressure; urodynamics; bladder biopsy; binding site; excitation; human; nonhuman; short survey; priority journal

RN (capsaicin) 404-86-4; (resiniferatoxin) 57444-62-9; (lidocaine) 137-58-6, 24847-67-4, 56934-02-2, 73-78-9; (alcohol) 64-17-5

L8 ANSWER 3 OF 8 EMBASE COPYRIGHT (c) 2007 Elsevier B.V. All rights reserved on STN

AN 1998269230 EMBASE

TI Use of intravesical capsaicin for urge urinary incontinence and irritative voiding syndromes.

AU Hussain I.F.; Fowler C.J.

CS I.F. Hussain, Department of Uro-Neurology, Natl Hospital Neurology Neurosurgery, Queen Square, London WC1N 3BZ, United Kingdom. i.hussain@ion.ucl.ac.uk

SO Current Opinion in Urology, (1998) Vol. 8, No. 4, pp. 293-296. .
Refs: 23
ISSN: 0963-0643 CODEN: CUOUEQ

CY United Kingdom

DT Journal; (Short Survey)

FS 002 Physiology
006 Internal Medicine
008 Neurology and Neurosurgery
028 Urology and Nephrology
030 Pharmacology
037 Drug Literature Index

LA English

SL English

ED Entered STN: 27 Aug 1998
Last Updated on STN: 27 Aug 1998

AB Intravesical capsaicin has been used in the management of selected patients with urge urinary incontinence throughout this decade, but the past 12 months has seen considerable interest in this and related compounds. It is no coincidence that during the same period the capsaicin receptor was cloned and named the vanilloid receptor subtype 1 and the European dual centre study of intravesical capsaicin reported that overall 80% of patients derived some clinical benefit. In spite of this, ultrapotent capsaicin analogues such as resiniferatoxin, which also interact with the vanilloid receptor subtype 1, are being studied. Preliminary reports of the potential advantages of intravesical resiniferatoxin are beginning to emerge, and in the future drugs that manipulate the vanilloid receptor may become universally important in the management of neurogenic overactive bladders.

CT Medical Descriptors:
*urge incontinence: TH, therapy
*micturition
neurogenic bladder: TH, therapy
muscle spindle afferent nerve
desensitization
spinal cord injury: TH, therapy
multiple sclerosis: TH, therapy
detrusor dyssynergia: CO, complication
detrusor dyssynergia: TH, therapy
bladder capacity
bladder pressure
urodynamics
bladder biopsy
binding site
excitation
human
nonhuman
short survey
priority journal
Drug Descriptors:
*capsaicin: DO, drug dose

*capsaicin: PD, pharmacology
vanilloid receptor
resiniferatoxin
lidocaine
alcohol
RN (capsaicin) 404-86-4; (resiniferatoxin) 57444-62-9; (lidocaine) 137-58-6, 24847-67-4, 56934-02-2, 73-78-9; (alcohol) 64-17-5

L8 ANSWER 4 OF 8 EMBASE COPYRIGHT (c) 2007 Elsevier B.V. All rights reserved on STN
AN 1998265824 EMBASE
TI Recent approaches to the treatment of urinary incontinence: A survey of patent activity from 1995 to 1998.
AU Butera J.A.; Argentieri T.M.
CS J.A. Butera, Cardiovascular/Metabolic Diseases, Wyeth-Ayerst Research, CN 8000, Princeton, NJ 08510-8000, United States
SO Expert Opinion on Therapeutic Patents, (1998) Vol. 8, No. 8, pp. 1017-1035. .
Refs: 80
ISSN: 1354-3776 CODEN: EOTPEG
CY United Kingdom
DT Journal; General Review
FS 028 Urology and Nephrology
030 Pharmacology
037 Drug Literature Index
LA English
SL English
ED Entered STN: 20 Aug 1998
Last Updated on STN: 20 Aug 1998
AB In its broadest sense, urinary incontinence (UI) is defined as involuntary loss of urine to such an extent as to become a hygienic or social concern to the patient [1]. Up to 50% of patients suffering from this disorder do not seek medical attention due to embarrassment or their willingness to accept the condition as a 'normal' course of ageing. Thus, incontinence often goes undiagnosed and untreated, and, in serious cases, may exact a staggering toll on the self-esteem and social and psychological outlook of those it affects. UI is usually classified into four types: stress, urge, overflow and functional. The first three types of UI refer to dysfunctions in either urine storage or urine emptying, while the latter occurs in patients with a relatively normal lower urinary tract, but who, nevertheless, suffer from severe cognitive impairment or immobility that precludes normal voiding behaviour. Much of the currently available pharmacological intervention includes the use of antimuscarinics/spasmolytics for the treatment of urinary urgency and sympathomimetics for the treatment of stress incontinence. Corrective measures could also involve behaviour modification, pelvic exercise or surgery. Due to significant, intolerable side-effects and/or limited efficacy associated with the current pharmacological approaches to UI treatment, patient compliance is low, resulting in a considerable unmet medical need for a new generation of more useful compounds. This comprehensive review examines the most recent claims for novel treatments of various forms of UI. Traditional approaches along the lines of novel antimuscarinics or novel formulations of currently used antimuscarinics are well represented. Importantly however, several new classes of agents with fewer side-effects have appeared which, if clinically successful, may represent. an exciting new frontier in the treatment of UI.
CT Medical Descriptors:
*urine incontinence: DT, drug therapy
*urine incontinence: TH, therapy
*bladder instability: DT, drug therapy
*detrusor dyssynergia: DT, drug therapy
*hyperreflexia: DT, drug therapy
patent
hormone substitution

human
review
Drug Descriptors:
*muscarinic receptor blocking agent: DT, drug therapy
*spasmolytic agent: DT, drug therapy
*tricyclic antidepressant agent: DT, drug therapy
*prostaglandin inhibitor: DT, drug therapy
*nonsteroid antiinflammatory agent: DT, drug therapy
*potassium channel stimulating agent: DT, drug therapy
*estrogen: DT, drug therapy
*serotonin 1a antagonist: DT, drug therapy
*amino acid receptor affecting agent: DT, drug therapy
*tachykinin receptor antagonist: DT, drug therapy
resiniferatoxin: DT, drug therapy
n [4 (4 acetamido 4 phenylpiperidino) 2 (3,4 dichlorophenyl)butyl] n methylbenzamide: DV, drug development
n [4 (4 acetamido 4 phenylpiperidino) 2 (3,4 dichlorophenyl)butyl] n methylbenzamide: DT, drug therapy
n [4 (4 acetamido 4 phenylpiperidino) 2 (3,4 dichlorophenyl)butyl] n methylbenzamide: PD, pharmacology
men 10627: DT, drug therapy
men 10627: PD, pharmacology
3' (2 amino 1 hydroxyethyl) 4' fluoromethanesulfonanilide: DV, drug development
3' (2 amino 1 hydroxyethyl) 4' fluoromethanesulfonanilide: DT, drug therapy
3' (2 amino 1 hydroxyethyl) 4' fluoromethanesulfonanilide: PD, pharmacology
oxybutynin: DT, drug therapy
tolterodine: DT, drug therapy
ephedrine: DT, drug therapy
phenylpropanolamine: DT, drug therapy
imipramine: DT, drug therapy
flavoxate: DT, drug therapy
buspirone: DT, drug therapy

RN (resiniferatoxin) 57444-62-9; (n [4 (4 acetamido 4 phenylpiperidino) 2 (3,4 dichlorophenyl)butyl] n methylbenzamide) 142001-63-6; (men 10627) 157351-81-0; (3' (2 amino 1 hydroxyethyl) 4' fluoromethanesulfonanilide) 137431-04-0; (oxybutynin) 1508-65-2, 5633-20-5; (tolterodine) 124937-51-5; (ephedrine) 299-42-3, 50-98-6; (phenylpropanolamine) 14838-15-4, 154-41-6, 4345-16-8, 48115-38-4; (imipramine) 113-52-0, 50-49-7; (flavoxate) 15301-69-6, 3717-88-2; (buspirone) 33386-08-2, 36505-84-7

CN (1) Sr 48968; Men 10627; Ns 49

CO (1) Pfizer; Lilly; Takeda

L8 ANSWER 5 OF 8 IMSDRUGNEWS COPYRIGHT 2007 IMSWORLD on STN

AN 1998:512 IMSDRUGNEWS

TI resiniferatoxin Afferon phase change II, USA, Europe (urinary incontinence)

SO R&D Focus Drug News (9 Feb 1998).

WC 113

TX A phase II investigation has been initiated in Europe and the USA with Afferon's vanilloid, resiniferatoxin (RTX), for the treatment of urge incontinence. This double-blind, placebo-controlled trial will involve 120 patients at four clinical sites and a single dose, administered into the bladder, is expected to be effective for several months. A preliminary clinical study in patients with urge incontinence due to neurological disorders has shown that RTX is capable of providing significant relief.

RTX acts as a neuronal desensitizing agent and is also being investigated in phase I/IIa trials for diabetic neuropathic pain. The agent is one of a series of capsaicin analogues acquired by Afferon from the US National Institutes of Health.

CN resiniferatoxin; RTX; RTX
RN 57444-62-9
CC G4B4 Urinary Incontinence Products; N2B Non-Narcotic Analgesics
CO Afferon
DSTA Phase II. United States; Europe
STA new drug; new phase

L8 ANSWER 6 OF 8 IPA COPYRIGHT (c) 2007 The Thomson Corporation on STN

AN 97:7104 IPA
DN 35-02639
TI Suppression of bladder hyperreflexia by intravesical resiniferatoxin
AU Cruz, F.; Guimaraes, M.; Silva, C.; Reis, M.
CS Inst. of Histol. and Embryol., Fac. of Med., 4200-Porto, Portugal
SO Lancet (England), (Aug 30 1997) Vol. 350, pp. 640-641. 5 Refs.
CODEN: LANCAO; ISSN: 0023-7507.
DT Letter
FS HUMAN
LA English
AB The effect of resiniferatoxin, an analog of capsaicin, on bladder hyperreflexia was studied in 7 patients with this condition who underwent urethral catheterization, after which 100 ml (or a volume equal to the bladder capacity when <100 ml) of a 50 nmol/l (n=3) or 100 nmol/l (n=4) alcoholic solution of resiniferatoxin was instilled and left inside the bladder for 30 min; all 7 patients had received intravesical capsaicin previously and 2 additional patients who had never received capsaicin before were also evaluated after therapy with 50 nmol/l resiniferatoxin.

In 5 patients, average urinary frequency, which ranged from 10-26 times per day before treatment, decreased to 6-12 times per day. This effect was detected as soon as the first day after treatment. Three patients were incontinent and became dry most days. Improvement was sustained up to 3 months, the longest follow-up available. A rise in maximum cystometric capacity (MCC) occurred in 4 of these patients. In a sixth patient a continuous increase in MCC was observed, but no clinical improvement was seen. In a seventh patient, no clinical or urodynamic improvement was seen. In the 2 previously untreated patients, both emptied their bladders by intermittent catheterization but still leaked due to non-voluntary contractions; discomfort evoked by treatment was minimum. One patient who received oxybutynin without successful results experienced continence on most days and increased MCC upon the addition of resiniferatoxin.
Ramune T. Dailide
SC 6 Drug Evaluations; 4 Toxicity
IT Resiniferatoxin; bladder diseases; hyperreflexia
IT Capsaicin; bladder diseases; hyperreflexia
IT Oxybutynin; concomitant therapy
IT Irritants; resiniferatoxin; bladder hyperreflexia
IT Bladder diseases; resiniferatoxin; hyperreflexia
IT Dosage; resiniferatoxin; bladder hyperreflexia
IT Drug administration routes; intravesical; resiniferatoxin
IT Toxicity; resiniferatoxin
IT Urinary incontinence; resiniferatoxin; intravesical
IT Irritants; capsaicin; bladder hyperreflexia
RN 57444-62-9 (Resiniferatoxin)
RN 404-86-4 (Capsaicin)
RN 5633-20-5 (Oxybutynin)

L8 ANSWER 7 OF 8 MEDLINE on STN
AN 1999011919 MEDLINE
DN PubMed ID: 9795827
TI Desensitization of bladder sensory fibers by intravesical capsaicin or capsaicin analogs. A new strategy for treatment of urge incontinence in

patients with spinal detrusor hyperreflexia or bladder hypersensitivity disorders.
AU Cruz F
CS Department of Urology, Hospital Sao Joao, Oporto, Portugal.
SO International urogynecology journal and pelvic floor dysfunction, (1998) Vol. 9, No. 4, pp. 214-20. Ref: 47
Journal code: 9514583. ISSN: 0937-3462.
CY ENGLAND: United Kingdom
DT Journal; Article; (JOURNAL ARTICLE)
(RESEARCH SUPPORT, NON-U.S. GOV'T)
General Review; (REVIEW)
LA English
FS Priority Journals
EM 199812
ED Entered STN: 15 Jan 1999
Last Updated on STN: 30 Oct 2002
Entered Medline: 22 Dec 1998
AB Recent experimental studies have identified a category of unmyelinated type C bladder afferent fibers in the pelvic nerves which are extremely sensitive to capsaicin. Sensory input conveyed by these fibers triggers a spinal reflex which, in chronic spinalized animals, facilitates and controls micturition. In addition, bladder C fibers were also shown to have a role in bladder pain perception. In humans capsaicin-sensitive afferent fibers also innervate the bladder and contribute to the reflexogenic control of the detrusor muscle and to bladder pain perception. Desensitization of such fibers by intravesical administration of capsaicin, presumably by blocking sensory transmission, has been shown to reduce involuntary micturition and to increase bladder capacity in patients with detrusor hyperreflexia of spinal origin, and to reduce the intensity of bladder pain in patients with bladder hypersensitivity. Very recently, resiniferatoxin, an ultrapotent capsaicin analog, was shown to have a similar clinical effect in this subset of patients. However, unlike capsaicin, resiniferatoxin did not evoke acute irritative urinary symptoms during bladder instillation.
CT Check Tags: Female
Administration, Intravesical
Animals
*Capsaicin: AD, administration & dosage
Capsaicin: TU, therapeutic use
Diterpenes: AD, administration & dosage
Diterpenes: TU,, therapeutic use
Humans
Nerve Fibers: DE, drug effects
Neurotoxins: AD, administration & dosage
Neurotoxins: TU, therapeutic use
*Urinary Bladder: IR, innervation
*Urinary Bladder, Neurogenic: DT, drug therapy
*Urinary Incontinence: DT, drug therapy
RN 404-86-4 (Capsaicin); 57444-62-9 (resiniferatoxin)
CN 0 (Diterpenes); 0 (Neurotoxins)

L8 ANSWER 8 OF 8 TOXCENTER COPYRIGHT 2007 ACS on STN
AN 1997:1919 TOXCENTER
CP Copyright (c) 2007 The Thomson Corporation
DN 35-02639
TI Suppression of bladder hyperreflexia by intravesical resiniferatoxin
AU Cruz, F.; Guimaraes, M.; Silva, C.; Reis, M.
CS Inst. of Histol. and Embryol., Fac. of Med., 4200-Porto, Portugal
SO Lancet (England), (Aug 30 1997) Vol. 350, pp. 640-641. 5 Refs.
CODEN: LANCAO. ISSN: 0023-7507.
DT Letter
FS IPA
OS IPA 97:7104
LA English
ED Entered STN: 16 Nov 2001

Last Updated on STN: 16 Nov 2001

AB The effect of resiniferatoxin, an analog of capsaicin, on bladder hyperreflexia was studied in 7 patients with this condition who underwent urethral catheterization, after which 100 ml (or a volume equal to the bladder capacity when <100 ml) of a 50 nmol/l (n=3) or 100 nmol/l (n=4) alcoholic solution of resiniferatoxin was instilled and left inside the bladder for 30 min; all 7 patients had received intravesical capsaicin previously and 2 additional patients who had never received capsaicin before were also evaluated after therapy with 50 nmol/l resiniferatoxin. In 5 patients, average urinary frequency, which ranged from 10-26 times per day before treatment, decreased to 6-12 times per day. This effect was detected as soon as the first day after treatment. Three patients were incontinent and became dry most days. Improvement was sustained up to 3 months, the longest follow-up available. A rise in maximum cystometric capacity (MCC) occurred in 4 of these patients. In a sixth patient a continuous increase in MCC was observed, but no clinical improvement was seen. In a seventh patient, no clinical or urodynamic improvement was seen. In the 2 previously untreated patients, both emptied their bladders by intermittent catheterization but still leaked due to non-voluntary contractions; discomfort evoked by treatment was minimum. One patient who received oxybutynin without successful results experienced continence on most days and increased MCC upon the addition of resiniferatoxin.
Ramune T. Dailide

SC 6 Drug Evaluations; 4 Toxicity

ST Miscellaneous Descriptors
Resiniferatoxin; bladder diseases; hyperreflexia
Capsaicin; bladder diseases; hyperreflexia
Oxybutynin; concomitant therapy
Irritants; resiniferatoxin; bladder hyperreflexia
Bladder diseases; resiniferatoxin; hyperreflexia
Dosage; resiniferatoxin; bladder hyperreflexia
Drug administration routes; intravesical; resiniferatoxin
Toxicity; resiniferatoxin
Urinary incontinence; resiniferatoxin; intravesical
Irritants; capsaicin; bladder hyperreflexia

RN 57444-62-9 (Resiniferatoxin)
404-86-4 (Capsaicin)
5633-20-5 (Oxybutynin)

=>

---Logging off of STN---

=>
Executing the logoff script...

=> LOG Y

COST IN U.S. DOLLARS	SINCE FILE ENTRY	TOTAL SESSION
FULL ESTIMATED COST	101.78	181.34

STN INTERNATIONAL LOGOFF AT 19:58:53 ON 06 MAR 2007